Supporting Information
for DOI: 10.1055/s-0036-1590906
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A convenient method for the synthesis of imidazo[1,2-\textit{a}]pyridines
with a new approach

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1. The procedure for the synthesis of 2-amino-5-(2-hydroxybenzoyl)nicotinonitrile (4a):
A mixture of 3-formyl chromone (1 mmol, 174 mg), malononitrile (1.2 mmol, 79 mg) and diammonium hydrogen phosphate (20% mol, 27 mg) were stirred in 6 ml H₂O at room temperature for 30 min, afterwards alkene was produced, and then was added to diammonium hydrogen phosphate (1 mmol, 27 mg), and finally, the reaction mixture was stirred at 50 °C for 3 hours. The obtained precipitate was filtered and washed with H₂O/EtOH.

The procedure for synthesis of 6-(2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (6a):
A mixture of 2-amino-5-(2-hydroxybenzoyl) nicotinonitrile (1 mmol, 239 mg) and phenacyl bromide (1 mmol, 199 mg) was stirred in 2 ml DMF for 4 hours under reflux condition. After completion of the reaction, water was added to the reaction mixture and the reaction mixture was extracted with dichloromethane. The organic phase was dried using sodium sulfate. Further purification was done using column chromatography (eluent; n-hexane: CH₂Cl₂ 1: 1).

6-(2-Hydroxybenzoyl)-2-phenylimidazo [1, 2-a] pyridine-8-carbonitrile (6a)
(176 mg, 52%) Colorless powder, m.p.= 198-200 °C; IR νmax(KBr, cm⁻¹): 3411, 2237, 1626, 1604; ¹HNMR (300 MHz, DMSO-d₆): δ = 6.99(t, 1H, J= 8.1 Hz, H-Ar), 7.01-7.04(d, 1H, J= 7.5Hz, H-Ar), 7.35-7.51(m, 5H, H-Ar), 7.97(d, 2H, J = 7.5 Hz, H-Ar), 8.20(brs, 1H, H-2-Pyridyl), 8.67(s, 1H, H-Imidazole), 9.22(d, 1H, J= 1.56 Hz, H-4-Pyridyl), 10.36(s, 1H, OH). ¹³CNMR (75 MHz, DMSO-d₆): δ = 99.6, 112.3, 115.2, 117.0, 119.5, 122.9, 124.2, 126.0, 129.0,
129.0, 130.5, 132.1, 132.3, 133.7, 136.1, 142.6, 146.9, 156.4, 192.0. Mass: HR-MS (ESI) = Calc. for C$_{21}$H$_{13}$N$_3$O$_2$ [M+H]$^+$ 340.1081 found 340.1083.

6-(5-Fluoro-2-hydroxybenzoyl)-2-phenylimidazo [1, 2-α] pyridine-8-carbonitrile (6b)
(211 mg, 59%) Colorless powder, m.p. = 240-241 °C; IR $\nu_{\text{max}}$(KBr, cm$^{-1}$): 3213, 2233, 1616, 1597; $^1$HNMR (300 MHz, DMSO-d$_6$): $\delta = 6.99$-7.04(m, 1H, H-Ar), 7.28-7.50(m, 5H, H-Ar), 7.97(d, 2H, $J$= 7.59 Hz, H-Ar), 8.24(s, 1H, H-2-Pyridyl), 8.67(s, 1H, H-Imidazole), 9.25(s, 1H, H-4-Pyridyl), 10.27(s, 1H, OH). $^{13}$CNMR (75 MHz, DMSO-d$_6$): $\delta = 99.7$, 112.3, 115.1, 115.8, 116.1, 118.2, 118.3($^2$J$_{C-F}$ = 7.5 Hz), 119.9, 120.2($^2$J$_{C-F}$ = 23.92 Hz), 122.4, 125.0, 125.1, 126.0, 128.9, 129.0, 132.0, 132.2, 136.5, 142.6, 147.0, 152.3, 153.6, 156.7 ($^1$J$_{C-F}$ = 234.75 Hz), 190.5. Mass: HR-MS (ESI) = Calc. for C$_{21}$H$_{12}$FN$_3$O$_2$ [M+H]$^+$ 358.0986 found 358.0989.

6-(5-Chloro-2-hydroxybenzoyl)-2-phenylimidazo [1, 2-α] pyridine-8-carbonitrile (6c)
(152 mg, 41%) Colorless powder, m.p. = 258-260 °C; IR $\nu_{\text{max}}$(KBr, cm$^{-1}$): 3400, 2231, 1632, 1590; $^1$HNMR (300 MHz, DMSO-d$_6$): $\delta = 7.02$-7.07(m, 1H, H-Ar), 7.38-7.49(m, 5H, H-Ar), 7.96(d, 2H, $J$= 7.14 Hz, H-Ar), 8.17(s, 1H, H-2-Pyridyl), 8.68(s, 1H, H-Imidazole), 9.20(s, 1H, H-4-Pyridyl). $^{13}$CNMR (75 MHz, DMSO-d$_6$): $\delta = 99.2$, 112.4, 115.3, 122.2, 126.0, 128.8, 129.0, 132.4, 142.7, 146.8. Mass: HR-MS (ESI) = Calc. for C$_{21}$H$_{12}$ClN$_3$O$_2$ [M+H]$^+$ 372.0545 found 372.0544.

6-(5-Bromo-2-hydroxybenzoyl)-2-phenylimidazo [1, 2-α] pyridine-8-carbonitrile (6d)
(187 mg, 45%) Colorless powder, m.p. = 243-244 °C; IR $\nu_{\text{max}}$(KBr, cm$^{-1}$): 3388, 2228, 1661, 1592; $^1$HNMR (300 MHz, DMSO-d$_6$): $\delta = 6.90$-6.92(m, 1H, H-Ar), 7.40-7.59(m, 5H, H-Ar), 7.87(brs, 2H, H-Ar), 8.12(s, 1H, H-2-Pyridyl), 8.47(s, 1H, H-Imidazole), 9.26(s, 1H, H-4-Pyridyl), 10.39(s, 1H, OH). $^{13}$CNMR (75 MHz, DMSO-d$_6$): $\delta = 89.0$, 110.4, 116.1, 118.9, 121.4, 127.6, 129.0, 131.7, 134.9, 144.0, 154.6, 155.8, 161.5, 190.2. Mass: HR-MS (ESI) = Calc. for C$_{21}$H$_{12}$BrN$_3$O$_2$ [M+H]$^+$ 416.0040 found 416.0040

2-(4-Chlorophenyl)-6-(5-fluoro-2-hydroxybenzoyl) imidazo [1, 2-α] pyridine-8-carbonitrile (6f)
(218 mg, 56%) Colorless powder, m.p. = 284-286 °C; IR $\nu_{\text{max}}$(KBr, cm$^{-1}$): 3403, 2237, 1637, 1585; $^1$HNMR (300 MHz, DMSO-d$_6$): $\delta = 6.99$-7.04(m, 1H, H-Ar), 7.26-7.36(m, 2H, H-Ar),
7.49(d, 2H, j= 8.55, H-Ar), 7.92-7.95(d, 2H, j= 8.52 Hz, H-Ar), 10.27(s, 1H, OH).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta = 99.7, 112.6, 115.0, 115.8, 116.1, 118.2, 118.3(J_{C-F}=75 \text{ Hz}),$
$119.9, 120.2(J_{C-F}= 23.25 \text{ Hz}), 122.5, 124.9, 125.0, 127.6, 129.0, 131.1. 132.1, 133.3, 136.4,$
$142.6, 145.7, 152.3, 153.6, 156.7(J_{C-F} = 234.9 \text{ Hz}), 190.4. \text{ Mass: HR-MS (ESI) = Calc. for }$
$C_{21}H_{12}FN_3O_2 [M+H]^+ 390.0451 \text{ found 390.0449.}$

2-(4-Bromophenyl)-6-(5-fluoro-2-hydroxybenzoyl) imidazo [1,2-a]pyridine-8-carbonitrile (6g)
(235 mg, 54%) Yellow powder, m.p.= 259-261°C; IR $\nu_{max}(KBr, \text{ cm}^{-1})$: 3402, 2225, 1674, 1593;

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 6.99-7.03(\text{m, 1H, H-Ar}), 7.26-7.37(\text{m, 2H, H-Ar}), 7.65(d,$
$2H, J= 8.34 \text{ Hz, H-Ar}), 7.90(d, 2H, J= 8.35 Hz, H-Ar), 8.24(s, 1H, H-2-Pyridyl), 8.68(s, 1H, H-
Imidazole), 9.24(s, 1H, H-4-Pyridyl), 10.27(s, 1H, OH).$ $^{13}$CNMR (75 MHz, DMSO-d$_6$): $\delta =$
$99.8, 112.7, 115.0, 115.8, 116.1, 118.2, 118.3(J_{C-F}= 7.2 \text{ Hz}), 120.0, 120.3(J_{C-F}= 24 \text{ Hz}), 122.0,$
$122.6, 124.9, 125.0, 127.9, 131.5, 131.9, 132.2, 136.5, 142.7, 145.8, 152.4, 153.6, 156.7(J_{C-F} =$
$234.75 \text{ Hz}), 190.5. \text{ Mass: HR-MS (ESI) = Calc. for } C_{21}H_{11}BrFN_3O_2 [M+H]^+ 436.0091 \text{ found 436.0094.}$

2-(4-Bromophenyl)-6-(5-fluoro-2-hydroxybenzoyl) imidazo [1,2-a]pyridine-8-carbonitrile (6g)
(235 mg, 54%) Yellow powder, m.p.= 259-261°C; IR $\nu_{max}(KBr, \text{ cm}^{-1})$: 3402, 2225, 1674, 1593;

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 6.99-7.03(\text{m, 1H, H-Ar}), 7.26-7.37(\text{m, 2H, H-Ar}), 7.65(d,$
$2H, J= 8.34 \text{ Hz, H-Ar}), 7.90(d, 2H, J= 8.35 Hz, H-Ar), 8.24(s, 1H, H-2-Pyridyl), 8.68(s, 1H, H-
Imidazole), 9.24(s, 1H, H-4-Pyridyl), 10.27(s, 1H, OH).$ $^{13}$CNMR (75 MHz, DMSO-d$_6$): $\delta =$
$99.8, 112.7, 115.0, 115.8, 116.1, 118.2, 118.3(J_{C-F}= 7.2 \text{ Hz}), 120.0, 120.3(J_{C-F}= 24 \text{ Hz}), 122.0,$
$122.6, 124.9, 125.0, 127.9, 131.5, 131.9, 132.2, 136.5, 142.7, 145.8, 152.4, 153.6, 156.7(J_{C-F} =$
$234.75 \text{ Hz}), 190.5. \text{ Mass: HR-MS (ESI) = Calc. for } C_{21}H_{11}BrFN_3O_2 [M+H]^+ 436.0091 \text{ found 436.0094.}$

Yellow crystal (polyhedron), dimensions 0.160 x 0.130 x 0.130 mm$^3$, crystal system monoclinic,
space group $P2_1/c$, $Z=4$, $a=8.5182(4) \text{ Å}, b=8.5756(4) \text{ Å}, c=24.0705(12) \text{ Å},$ alpha=90 deg,
beta=94.4088(8) deg, gamma=90 deg, $V=1753.12(15) \text{ Å}^3$, rho=1.653 g/cm$^3$, $T=200(2) \text{ K,}$
Theta$_{max}$= 28.313 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD
area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of
3.92and a completeness of 99.8% to a resolution of 0.75 Å, 17588 reflections measured, 4356
unique (R(int)=0.0291), 3370 observed (I > 2$\sigma$(I)), intensities were corrected for Lorentz and
polarization effects, an empirical scaling and absorption correction was applied using SADABS$^1$
based on the Laue symmetry of the reciprocal space, mu=2.38mm$^{-1}$, $T_{min}=0.90, T_{max}=0.97,$
structure refined against $F^2$ with a Full-matrix least-squares algorithm using the SHELXL-2016/6
(Sheldrick, 2016) software $^2$, 257 parameters refined, hydrogen atoms were treated using
appropriate riding models, except H32 of the hydroxy group, which was refined isotropically,
goodness of fit 1.04 for observed reflections, final residual values R1(F)=0.034, wR(F$^2$)=0.082
for observed reflections, residual electron density -0.68 to 0.72 eÅ$^-3$. CCDC 1557527 contains
the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

2-(4-Bromophenyl)-6-(5-chloro-2-hydroxybenzoyl) imidazo [1, 2-a] pyridine-8-carbonitrile (6h)

(240 mg, 53%)

Colorless powder, m.p. = 252-254°C; IR ν_max(KBr, cm⁻¹): 3391, 2228, 1661, 1592; ¹HNMR (300 MHz, DMSO-d_6): δ = 6.94-7.04(m, 1H, H-Ar), 7.39-7.51(m, 2H, H-Ar), 7.66(d, 2H, J = 8.25 Hz, H-Ar), 7.90(d, 2H, J = 8.26 Hz, H-Ar), 8.24(s, 1H, H-2-Pyridyl), 8.67(s, 1H, H-Imidazole), 9.25(s, 1H, H-4-Pyridyl), 10.49(s, 1H, OH). ¹³CNMR (75 MHz, DMSO-d_6): δ = 99.8, 112.7, 115.0, 118.7, 122.0, 122.6, 123.0, 125.1, 128.0, 129.3, 131.5, 131.9, 132.2, 132.8, 136.5, 142.7, 145.8, 154.8, 190.3. Mass: HR-MS (ESI) = Calc. for C_{21}H_{11}^{79}Br^{35}ClN_{3}O_{2} [M+H]^+ 451.9796 found 451.9798.
6-(2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (6a)

$\text{OH}$

$\text{O}$

$\text{CN}$

1H NMR of 6a (300 MH, DMSO-d6)
$^1$H NMR of 6a (300 MH, DMSO-d6)

$^{13}$C NMR of 6a (75 MH, DMSO-d6)
HRMS(ESI) of 6a

IR (KBr, cm$^{-1}$) of 6a
6-(5-fluoro-2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (6b)

\[ \text{\(6\text{b}\)} \]

\( ^1H \text{NMR of } 6\text{b} \) (300 MH, DMSO-d6)
$^1$H NMR of 6b (300 MH, DMSO-d6)

$^{13}$C NMR of 6b (75 MH, DMSO-d6)
$^{13}\text{C NMR of } 6\text{b (75 MH, DMSO-d6)}$

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![HRMS(ESI) of 6b]
IR (KBr, cm\(^{-1}\)) of \(6b\)

6-(5-chloro-2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (\(6c\))

\[\text{\begin{center} \includegraphics[width=0.3\textwidth]{image} \end{center} }\]

\(^1\text{H NMR of } 6c\ (300 \text{ MH, DMSO-d6})\)
$^{13}$C NMR of 6c (75 MH, DMSO-d6)

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IR (KBr, cm$^{-1}$) of 6c

6-(5-bromo-2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitrile (6d)

$^1$H NMR of 6d (300 MH, DMSO-d6)
$^1$H NMR of 6d (300 MH, DMSO-d6)

$^{13}$C NMR of 6d (75 MH, DMSO-d6)
HRMS(ESI) of 6d

IR (KBr, cm⁻¹) of 6d
6-(5-fluoro-2-hydroxybenzoyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-8-carbonitrile (6e)

HRMS(ESI) of 6e
2-(4-chlorophenyl)-6-(5-fluoro-2-hydroxybenzoyl)imidazo[1,2-a]pyridine-8-carbonitrile (6f)

\[
\text{\textsuperscript{1}H NMR of 6f (300 MH, DMSO-d6)}
\]
$^1$H NMR of 6f (300 MH, DMSO-d6)

$^{13}$C NMR of 6f (75 MH, DMSO-d6)
$^{13}$C NMR of 6f (75 MH, DMSO-d6)

HRMS(ESI) of 6f
IR (KBr, cm$^{-1}$) of 6f

2-(4-bromophenyl)-6-(5-fluoro-2-hydroxybenzoyl)imidazo[1,2-a]pyridine-8-carbonitrile (2g)

$^{1}$H NMR of 6g (300 MH, DMSO-d6)
$^1$H NMR of 6g (300 MH, DMSO-d6)

$^{13}$C NMR of 6g (75 MH, DMSO-d6)
HRMS(ESI) of 6g

IR (KBr, cm⁻¹) of 6g
2-(4-bromophenyl)-6-(5-chloro-2-hydroxybenzoyl)imidazo[1,2-a]pyridine-8-carbonitrile (6h)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Cl} & \quad \text{CN} \\
\text{N} & \quad \text{N} \\
\text{Br} & \quad \text{N}
\end{align*}
\]

\(^1\)H NMR of 6h (300 MH, DMSO-d6)
$^{13}$C NMR of $6h$ (75 MH, DMSO-d6)

HRMS(ESI) of $6h$
IR (KBr, cm$^{-1}$) of 6h
**Fig. 1.** The structures of some bioactive compounds with imidazo[1,2-α]pyridine skeleton

- **Zolpidem (anti-insomnia)**: $R_1 = R_2 = R_3 = \text{CH}_3$
- **Necopidem (sedative)**: $R_1 = \text{CH}_3$, $R_2 = \text{C}_2\text{H}_5$, $R_3 = \text{i-C}_3\text{H}_7$
- **Alpidem (anxyolitic)**: $R_1 = R_2 = \text{Cl}$, $R_3 = \text{n-C}_3\text{H}_7$
- **Saripidem (anxyolitic)**: $R_1 = \text{H}$, $R_2 = \text{Cl}$, $R_3 = \text{C}_2\text{H}_5$
- **Olprinone (heart-failure drug)**
- **Bromodomain inhibitor**
- **CENP-E inhibitor**

Anticancer
Fig 2. ORTEP diagram of the X-ray crystal structure of 6g
Scheme 1. The synthesis of functionalized 2-phenylimidazo[1,2-a]pyridine 6a-h
Scheme 2. Synthesis of functionalized 2-aminopyridines through three-component reaction in water
Scheme 3. The proposed mechanism for the synthesis of 6-(2-hydroxybenzoyl)-2-phenylimidazo[1,2-a]pyridine-8-carbonitriles 6a-h
Table 1. The optimization of the condensation reaction of phenacyl bromide and 2-amino-5-(2-hydroxybenzoyl)nicotinonitrile to access 6a

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</tbody>
</table>
Table 2. The synthesis of derivatives of 2-phenylimidazo[1,2-a]pyridine

\[
\begin{array}{c}
\text{1a-d} \quad X: \text{H, F, Cl, Br} \\
\text{2} \\
\text{3} \quad \text{H}_2\text{O, 50°C} \\
\text{5a-d} \quad \text{BrO}_2 \quad \text{Ar} \\
\text{4a-d} \\
\text{6a-h} \\
\text{Ar: Ph, 4-F-C}_6\text{H}_4, \\
\text{4-Cl-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4
\end{array}
\]
checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: sba148

Bond precision: C-C = 0.0028 Å Wavelength=0.71073

Cell: a=8.5182(4) b=8.5756(4) c=24.0705(12)
alpha=90 beta=94.4088(8) gamma=90

Temperature: 200 K

Calculated Reported
Volume 1753.12(15) 1753.12(15)
Space group P 21/c P 21/c
Hall group -P 2ybc -P 2ybc
Moiety formula C21 H11 Br F N3 O2 ?
Sum formula C21 H11 Br F N3 O2 C21 H11 Br F N3 O2
Mr 436.23 436.24
Dx,g cm⁻³ 1.653 1.653
Z 4 4
Mu (mm⁻¹) 2.378 2.378
F000 872.0 872.0
F000’ 871.23
h,k,lmax 11,11,32 11,11,32
Nref 4366 4356
Tmin,Tmax 0.697,0.734 0.899,0.972
Tmin’ 0.677

Correction method= # Reported T Limits: Tmin=0.899 Tmax=0.972
AbsCorr = MULTI-SCAN

Data completeness= 0.998 Theta(max)= 28.313
R(reflections)= 0.0344( 3370) wR2(reflections)= 0.0895( 4356)
S = 1.045 Npar= 257

The following ALERTS were generated. Each ALERT has the format test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.
Alert level C
ABSTY02_ALERT_1_C  An _exptl_absorpt_correction_type has been given without
a literature citation. This should be contained in the
_exptl_absorpt_process_details field.
Absorption correction given as multi-scan

Alert level G
PLAT012_ALERT_1_G N.O.K. _shelx_res_checksum found in CIF ........ Please Check
PLAT432_ALERT_2_G Short Inter X...Y Contact F35 .. C22 .. 2.94 Ang.
PLAT432_ALERT_2_G Short Inter X...Y Contact O1 .. C17 .. 2.97 Ang.
PLAT434_ALERT_2_G Short Inter HL...HL Contact Br1 .. F35 .. 3.14 Ang.

0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
1 ALERT level C = Check. Ensure it is not caused by an omission or oversight
4 ALERT level G = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
3 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low
0 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the
minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement
strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more
serious problems it may be necessary to carry out additional measurements or structure
refinements. However, the purpose of your study may justify the reported deviations and the more
serious of these should normally be commented upon in the discussion or experimental section of a
paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify
outliers and unusual parameters, but every test has its limitations and alerts that are not important
in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no
aspects of the results needing attention. It is up to the individual to critically assess their own
results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs
submitted for publication in IUCr journals (Acta Crystallographica, Journal of Applied
Crystallography, Journal of Synchrotron Radiation); however, if you intend to submit to Acta
Crystallographica Section C or E or IUCrData, you should make sure that full publication checks
are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the Notes for Authors of the relevant journal for any special instructions relating to
CIF submission.

PLATON version of 24/11/2016; check.def file version of 23/11/2016